

Upper Respiratory Tract Tumors in Cpb:WU (Wistar Random) Rats

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A survey is given of upper respiratory tract tumors in Cpb:WU (Wistar random) rats. Data were collected from ten 24- to 30-month toxicity/carcinogenicity studies and from one 12-month study. Nasal tumors may lead to dyspnea, mouth breathing, and nasal discharge. These clinical signs mainly occurred in rats bearing squamous cell carcinomas. The large nasal tumors were often osteolytic, they invaded the subcutis over the premaxilla, resulting in swellings on the back of the nose, and extended into the brain. The incidence of nasal tumors in untreated male controls was 1.1% (7/661), the tumors invariably being squamous cell carcinomas. There were no nasal tumors found in untreated female controls. The type of compound-induced nasal tumor most frequently observed was adenocarcinoma (of the olfactory epithelium) followed, in order of decreasing incidence, by squamous cell carcinoma, carcinoma *in situ*, polypoid adenoma, Schwannoma, and carcinosarcoma. It was proposed that adenocarcinomas of the olfactory epithelium should be classified as neuroepitheliomas. It was also suggested that squamous cell carcinomas, seen in association with necrotizing inflammation of an incisor tooth, should be considered as part of the malocclusion syndrome. No spontaneous tracheal tumors were observed, and only one out of 422 untreated female controls (0.2%) was seen to have a laryngeal tumor, an adenoma. Induced laryngeal tumors included carcinoma *in situ*, squamous cell carcinoma, and adenocarcinoma. Squamous cell carcinoma was the only type of treatment-related tracheal tumor found. The incidences of induced laryngeal and tracheal tumors were very low, and in no case were these tumors statistically significantly different from the respective incidences in controls.

Introduction

An increasing number of chemicals appear to be capable of inducing upper respiratory tract tumors in rodents. Nasal tumors are encountered most frequently (1-3), laryngeal tumors occur much less frequently, and tracheal tumors are relatively rare. Data on incidence and morphology of spontaneous and induced upper respiratory tract tumors are valuable as background information and may be helpful for the evaluation and interpretation of the results of future studies.

In our laboratory the Cpb:WU (Wistar random) rat has been used in short- and long-term oral and inhalation studies since 1972. The present paper deals with the incidence and type of upper respiratory tract tumors found in ten long-term (24- to 30-month) oral or inhalation studies and in one 12-month inhalation study using this strain of rats. Only studies in which a detailed histopathological examination of the nose, larynx, and/or trachea was performed were included in this survey.

Materials and Methods

For the present survey, data were collected from ten long-term (24- to 30-month) toxicity/carcinogenicity studies with seven different compounds (Table 1) and from one 12-month inhalation study with vinyl chloride monomer (4) using Cpb:WU (Wistar random) rats. For the sake of comparability of the data, findings in control animals used in the 12-month vinyl chloride study were not included in this survey.

The rats were from a closed colony and were bred at random under SPF-conditions; they were obtained from the TNO Central Institute for the Breeding of Laboratory Animals, Zeist, the Netherlands. At the start of the studies the rats were 4 to 7 weeks old; they were given the Institute's grain-based stock diet and unfluoridated tap water *ad libitum*. In the inhalation studies, neither food nor water were available to the animals during exposure.

The nose, larynx, and trachea were preserved in an aqueous neutral phosphate-buffered 4% formaldehyde solution, processed through paraffin wax (the noses after decalcification in nitric acid), sectioned at 5 μ m (noses at four or six standard cross levels), stained with hematoxylin and eosin, and examined by light microscopy. Special staining methods were applied when

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Table 1. Compounds tested, route of administration, study duration, and number of controls used in long-term studies included in the present survey on upper respiratory tract tumors in Cpb:WU (Wistar random) rats.

Compound	Route	Duration, months	Initial no. of controls		Effective no. of rats						Reference
					Males			Females			
			Male	Female	Nose	Larynx	Trachea	Nose	Larynx	Trachea	
A ^a	Inh.	24	100	100	98	93	98	97	88	100	
Methylbromide	Inh.	29	50	60	46	47	48	58	54	60	(5,6)
1,2-Propylene oxide	Inh.	28	70	70	66	68	68	64	64	67	(7)
2,3,4-Trichlorobutene-1	Inh.	25	100	100	89	86	97	95	89	99	(8)
B ^a	Inh.	24	60	60	60	60	59	60	58	59	
Formaldehyde	Inh.	30	135		134	NC ^b	NC				(9)
Formaldehyde	Inh.	28	60		52	NC	NC				(10,11)
Acetaldehyde	Inh.	28	55	55	49	50	50	50	51	51	(12,13)
Acetaldehyde	Inh.	24	20	20	18	16	16	18	18	18	(14)
Formaldehyde	Oral	24	50	50	49	NC	NC	50	NC	NC	(15)
Total no. of rats			700	515	661	420	436	492	422	454	

^aIndustrial compounds of which the identity and specifications are known to the authors. The studies have been described in confidential reports; neither compound was found to induce upper respiratory tract tumors.

^bNC = not collected.

indicated. A few nasal tumors were examined by electron microscopy using ultrathin sections stained with uranyl acetate and lead citrate.

Results and Discussion

Nose

Clinical Signs and Gross Pathology of Nasal Tumors. A rapidly expanding swelling on the back of the nose was often seen as an indication of a nasal tumor (Plate 1). Rats bearing acetaldehyde-induced nasal tumors often showed dyspnea; mouth breathing; and a bloody, greenish, pus-like nasal discharge (12). Nasal discharge and mouth breathing were only rarely seen in rats with trichlorobutene- or vinyl chloride-induced carcinomas of the olfactory epithelium (4,8). This distinct difference in clinical symptoms between acetaldehyde-treated rats, on the one hand, and vinyl chloride- and trichlorobutene-exposed rats, on the other hand, may be explained by the fact that the nose of acetaldehyde-exposed rats was often partially or entirely occluded by either a tumor or a plug of keratin (with or without inflammatory exudate) formed by severely hyperkeratotic metaplastic nasal respiratory epithelium. In contrast, the nasal respiratory epithelium in vinyl chloride- and trichlorobutene-exposed rats was apparently normal or only slightly affected (4,8).

The gross nasal lesions ranged from small thickenings on the back of the nose to large protrusions measuring 2 × 2 cm. The tumors were grayish white, varied from soft to relatively firm, partially or completely filled the nasal cavity, perforated bones, infiltrated the subcutis, and extended into the brain (Plate 2). We have the impression that squamous cell carcinomas of the respiratory epithelium mainly invade the subcutis, while carcinomas of the olfactory epithelium extend both into the subcutis and the brain. For a more general descrip-

tion of clinical signs and gross pathology of nasal tumors in rodents, including data from the literature, the reader is referred to one of our recent papers (2).

Nasal Tumors in Untreated Controls. Seven out of a total of 661 untreated male control animals (1.1%) were found to bear a nasal tumor with the incidence in the various control groups ranging from 0 (0/98) to 3.4% (3/89). Nasal tumors were not encountered in any of the 492 untreated female control rats. Nasal tumors in male controls were invariably squamous cell carcinomas. Six of the latter neoplasms were large, unilateral, well-differentiated keratinized squamous cell carcinomas, located in the anterior half of the nose; they had destroyed turbinates and bones, and extended into the subcutis. Three of these large carcinomas were clearly associated with odontodystrophy, severe necrotizing (peri)odontitis and rhinitis. Two other large tumors grew around one of the incisor teeth, but in both cases the tooth was not clearly inflamed or necrotic. In the sixth case no incisor tooth was seen to be involved in the tumor process. Finally, one small infiltrating squamous cell carcinoma was seen in an inflamed nasolachrymal duct. One of the large tumors had metastasized to the lungs.

The site of origin of the large nasal tumors is generally uncertain, although they most likely are derived from (metaplastic) respiratory epithelium lining the anterior sinonasal structures. The number of nasal squamous cell carcinomas found in treated rats, but considered to be unrelated to treatment, was 1.2% (13/1100) for males and 0.2% (2/900) for females. Other types of spontaneous nasal tumors detected in these treated rats included 1 carcinoma *in situ*, 1 osteosarcoma, 1 fibrosarcoma, and 4 odontogenic tumors in males and 1 papilloma in a female.

Induced Nasal Tumors. Nasal tumors induced in Cpb:WU (Wistar random) rats are listed in Table 2.

SQUAMOUS CELL CARCINOMA. Acetaldehyde-induced squamous cell carcinomas varied from large tumors, filling one or both sides of the nasal cavity, destroying

Table 2. Induced nasal tumors in Cpb:WU(Wistar random) rats.

Tumor type	Chemical
Squamous cell carcinoma	Formaldehyde, acetaldehyde
Carcinoma <i>in situ</i>	Acetaldehyde
Polypoid adenoma	Formaldehyde
Adenocarcinoma	Vinyl chloride, trichlorobutene, acetaldehyde
Carcinosarcoma	Vinyl chloride
Schwannoma	Trichlorobutene

turbinates and bones and extending into the subcutis and brain, to small neoplasms invading the submucosa of the nasal epithelium (12). The large tumors often showed extensive keratinization, and their origin could not be determined.

Most small squamous cell carcinomas were seen to originate from metaplastic, keratinized, stratified squamous respiratory epithelium, and they occurred in the anterior part of the nose. A few squamous cell carcinomas appeared to be derived from metaplastic, keratinized, squamous olfactory epithelium located in the dorsomedial and posterior part of the nasal cavity (13).

Formaldehyde-induced squamous cell carcinomas were relatively large keratinizing or nonkeratinizing tumors originating from the naso- and maxilloturbinates or from the lateral wall at the level of these turbinates (Plate 3); they invariably invaded bones and/or the subcutis (9). Squamous cell carcinomas of the respiratory epithelium were also found in Cpb:WU (Wistar random) rats with their respiratory mucosa severely damaged by electrocoagulation and exposure to 10 ppm formaldehyde for 28 months (11). The only squamous cell carcinoma found to have metastasized to the lungs was present in a rat exposed to acetaldehyde (Plate 4).

CARCINOMA *IN SITU*. In several rats exposed to high concentrations of acetaldehyde (1500 or 3000 ppm) carcinomas *in situ* developed in metaplastic stratified squamous respiratory epithelium (13). Clearly, these tumors were part of the neoplastic response of the nasal respiratory epithelium to acetaldehyde and may be considered precursors of the frequently found squamous cell carcinomas.

POLYPOID ADENOMA. A total of four polypoid adenomas was observed in our strain of rats, namely two in male rats exposed to 20 ppm formaldehyde for 4 and 8 weeks, respectively, followed by an observation period of over 2 years (10); one in a male rat exposed to 10 ppm formaldehyde for 3 months, followed by an observation period of 25 months (11); and one in a male rat exposed to 1.5/2.0 ppm trichlorobutene for 83 weeks (8). Those seen after exposure to 20 ppm formaldehyde are considered compound induced, while those seen in the other studies may or may not be treatment related. We never saw a polypoid adenoma in an untreated control rat.

One of the formaldehyde-related tumors was derived from the epithelium lining the maxilloturbinate and the adjacent lateral wall; it was an exophytic sessile tumor protruding into the nasal cavity (Plates 5 and 6). The other formaldehyde-induced tumor was a small

pedunculated adenoma, originating from the lateral wall at the level of the nasoturbinate. In addition to solid sheets of epithelial cells and microcysts, the latter neoplasm contained one large cystic structure partially lined by keratinized stratified squamous epithelium. A third polypoid adenoma, possibly related to formaldehyde exposure, was a small pedunculated adenoma, derived from the ventral margin of the nasoturbinate. The polypoid adenoma found in a trichlorobutene-exposed rat was an exophytic sessile adenoma, arising from the respiratory epithelium lining the lateral aspect of the nasoturbinate and lateral wall. The diagnosis of polypoid adenoma was based on the criteria described by Kerns (16). In view of tumors' localization, histology, and cytology, there seems to be little doubt that polypoid adenomas originate from respiratory epithelium. Ultrastructural studies (16) demonstrate that these tumors have the characteristics of respiratory epithelium (17).

ADENOCARCINOMA. There were no obvious differences in the gross and microscopic appearance between adenocarcinomas induced by vinyl chloride (4), trichlorobutene (8), or acetaldehyde (13).

Adenocarcinomas varied in size from small groups of atypical cells to large tumors. Small atypical foci were located in the lamina propria of the olfactory epithelium, grew endophytically along the structures of the nasal passages, and invaded nerve bundles (Plate 7). Large osteolytic exophytic tumors (Plate 8) with large areas of necrosis grew outside the nasal cavity into the subcutis and the cerebrum via the olfactory lobe (Plate 9). The tumors consisted of compact sheets and cords of cells separated by strands of fibrous tissue widely varying in thickness. Tumor cells were pleomorphic, and bizarre mitotic figures were often observed. Tumors often contained both dark and light cells (Plate 8) with big hyperchromatic round-to-oval nuclei. Dark cells were small with scanty cytoplasm, sharp nuclear membranes, a fine nuclear chromatin pattern, and small, distinct nucleoli. Several tumors exhibited rosettes, pseudorosettes, and palisading and glandular formations, suggesting a neurogenic origin (Plates 10-12). Metastases were seen in three cases; two tumors had metastasized to cervical lymph nodes and one tumor, to the lungs (13).

From electron microscopic studies performed on acetaldehyde-induced adenocarcinomas, it was found that the cytoplasm of the tumor cells contained small mitochondria, a few cisternae of rough endoplasmic reticulum, and many free polyribosomes, but they contained no unique structures. Nuclei were big and indented and had large compact nucleoli. Desmosomelike structures occurred between adjacent cells. Neurofibrils could not be identified. The overall picture pointed to the basal cells of the olfactory epithelium as the cells of origin. This cell type has been suggested as the stem cell from which olfactory sustentacular cells develop. In view of their localization, prevailing histologic pattern, and cytology, the nasal adenocarcinomas are considered to be derived from olfactory stem cells or sustentacular cells.

A number of investigators have reported neuroepitheliomas, esthesioneuroepitheliomas, (esthesio)neuroblastomas, esthesioneuromas, or esthesioneurocytomas of the nasal olfactory epithelium in experimental animals treated with carcinogens (2). The neurogenic origin of esthesioneuroepitheliomas should appear from the unequivocal presence of neurotubules, neurosecretory granules, or neuritic processes of tumor cells (18-21). Neuroblasts are supposedly the precursor cells from which olfactory sensory cells differentiate during embryonic development (22,23). Atrophy and toxic degeneration of olfactory sensory cells could create a stimulus for stem cells to proliferate. In addition, tumors classified as poorly differentiated adenocarcinomas may originate from neuroblasts that have lost their characteristic morphological markers (e.g., neurotubules, axons), and in this case, they are probably of neurogenic origin and should be classified as esthesioneuroepitheliomas. On the other hand, poorly differentiated adenocarcinomas exhibiting rosettes and pseudorosettes may have been misdiagnosed as esthesioneuroepitheliomas. Rivenston et al. (24) proposed to classify all tumors from the olfactory epithelium as neuroepitheliomas, arguing that calling sustentacular and basal cells nonneurogenic would, with respect to the nervous system, imply the need to remove all gliomas from the neurogenic tumor group. Further subclassification of nasal neuroepitheliomas could then be based on the prevailing type of tumor cells.

Relevant to the discussion on classification and nomenclature of tumors of the olfactory epithelium, may be an observation we made in a study into the recovery of severe acetaldehyde-induced damage to the olfactory epithelium of rats (14). Immediately after the termination of the exposure to acetaldehyde, the dorsomedial part of the nose normally lined by olfactory epithelium was seen to be covered by uni- or multilayered basal cells. During the recovery period these undifferentiated cells were seen to differentiate into groups of sensory cells accompanied by the formation of nerve bundles (Plate 13). This striking finding supports the view of Graziadei and Monti Graziadei (22,23) that basal cells are the stem cells of the sensory neurons, and it also supports Rivenston's suggestion (24) to classify all types of tumors derived from the olfactory epithelium as neuroepitheliomas.

A male rat exposed to 5000 ppm vinyl chloride for 52 weeks (4) was found to have a nasal tumor nearly completely consisting of columnar cells arranged in rosettes. The spaces lined by the tall cells often contained eosinophilic material. This histological appearance is highly suggestive of an esthesioneuroepithelioma (Plate 14).

CARCINOSARCOMA. One carcinosarcoma was found in a female rat exposed to 5000 ppm vinyl chloride (4). In this tumor sarcomatous structures predominated, although tumorous epithelial elements were also present.

SCHWANNOMA. Three male rats exposed to 1.5/2.0 ppm trichlorobutene bore nasal tumors which were diagnosed as malignant Schwannomas (8). Two of the tumors

were very large osteolytic masses growing outside the nasal cavity, while the third was a limited tumorous process expanding in the olfactory lamina propria. The diagnosis was based mainly on the involvement of mucosal nerve bundles, and the typical histologic picture showing whorls of plump spindle or epithelioid cells and circumscribed fibrous areas.

MALOCCLUSION SYNDROME. The rat incisor teeth develop from cells that are derived from a continuously proliferating elliptical sheath, the odontogenic epithelium, which is located at the base of the tooth and which encloses the connective tissue of the primitive pulp. An adult incisor tooth undergoes functional attrition as a normal wearing process. When, by reason of accident, one of the incisors is broken or when a malocclusion occurs the nonattrition of the opposing incisor and its continuous growth results in an elongation or overgrowth; the term "overgrowth" is misleading as, in reality, this elongation is not related to the rate of growth of the tooth but is the result of the lack of wear (25).

The malocclusion syndrome, which occurs in about 10% of Cpb:WU (Wistar random) rats, is very frequently accompanied by odontitis, periodontitis, sinus maxillaris sinusitis, and rhinitis. It is reasonable to assume that a condition of severe necrotizing (peri)odontitis which involves the whole area of the incisor tooth, the maxillary turbinate, and the sinus maxillaris may enhance the risk of the development of squamous cell carcinoma or odontoblastoma, originating from metaplastic respiratory or odontogenic epithelium, respectively. In three of the seven untreated controls with a nasal squamous cell carcinoma, the tumor was seen to be associated with severe necrotizing periodontitis and rhinitis, indicating that this condition of chronic irritation is probably associated with the formation of some of the nasal tumors found in our strain of rats. Moreover, two other squamous cell carcinomas found in the controls grew around an incisor tooth that, however, was not clearly necrotic or inflamed. It is possible that in rats, nasal squamous cell carcinomas could be considered part of the malocclusion syndrome in some instances. Since inflammatory reactions such as odontitis, periodontitis, and rhinitis are accompanied by recurrent tissue damage and repair, which are known to predispose to tumor formation in other locations, rats suffering from the malocclusion syndrome may be more susceptible to nasal carcinogens than normal rats.

Larynx and Trachea.

TUMORS IN UNTREATED CONTROLS. None of 420 untreated male controls and 1 of 422 untreated female controls (0.2%) were found to have a laryngeal tumor. The latter tumor was a small adenoma. No tracheal tumors were observed in 436 male and 454 female control rats.

INDUCED TUMORS. Laryngeal tumors observed in exposed rats included a carcinoma *in situ* in 1/47 females exposed to 1500 ppm acetaldehyde (Plate 15), squamous cell carcinomas in 1/68 males exposed to 300 ppm propylene oxide, and 1/18 females exposed to 1500 ppm acetaldehyde, and an adenocarcinoma in 1/68 males exposed to 300 ppm propylene oxide. Despite the low

incidence of these tumors, they were all considered to be compound induced.

Squamous cell carcinoma was the only type of treatment-related tumor observed in the trachea. One such tumor was seen in a group of 96 females exposed to 1.5/2 ppm trichlorobutene, and another one was found in a group of 68 males exposed to 300 ppm propylene oxide.

Concluding Remarks

Nasal tumors in untreated control rats were only found in males, and were invariably squamous cell carcinomas.

In order of decreasing incidence the following types of induced nasal tumors were seen: adenocarcinoma (of the olfactory epithelium), squamous cell carcinoma, carcinoma *in situ*, polypoid adenoma, Schwannoma and carcinosarcoma.

It was proposed that adenocarcinomas of the olfactory epithelium might be best classified as neuroepitheliomas.

The suggestion was made to regard squamous cell carcinomas found in untreated controls in association with dystrophy and necrotizing inflammation of incisor teeth as part of the malocclusion syndrome.

Both spontaneous and induced laryngeal and tracheal tumors were very rare.

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PLATE 1. Deformed nose due to nasal adenocarcinoma of the olfactory epithelium extending into the subcutis over the premaxilla; male rat exposed to 750 ppm acetaldehyde for 28 months.

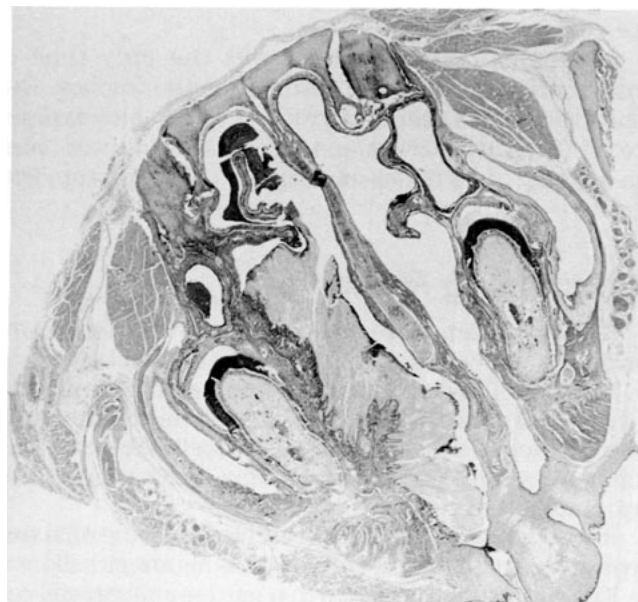


PLATE 3. Keratinized squamous cell carcinoma from the lateral wall; male rat exposed to 20 ppm formaldehyde for 13 weeks and killed after a recovery period of over 2 years. H&E, $\times 10$.



PLATE 2. Nasal adenocarcinoma of the olfactory epithelium extending into the subcutis and the brain; male rat exposed to 1.5/2 ppm trichlorobutene for 83 weeks.

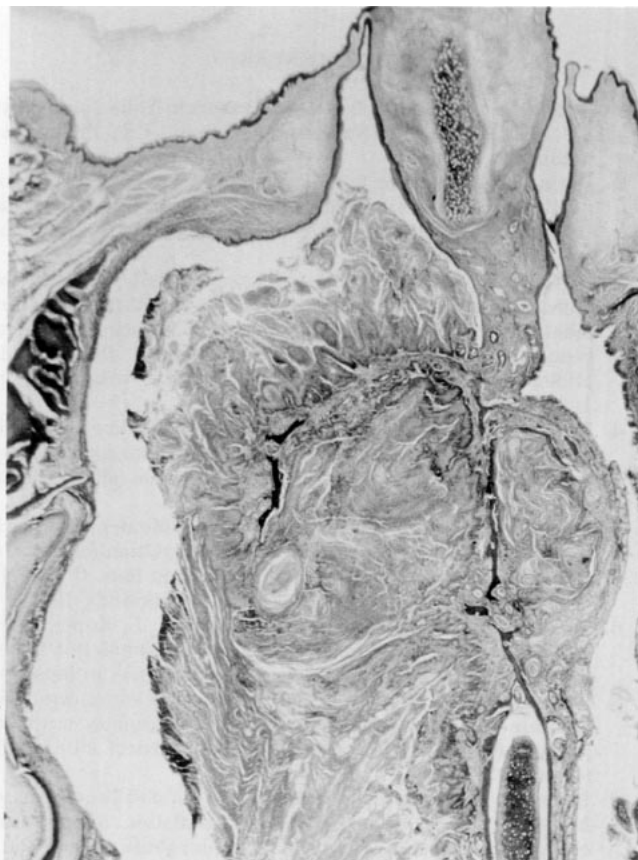


PLATE 4. Severely keratinized squamous cell carcinoma of the nasal septum, which had metastasized to the lungs of a male rat exposed to 1500/3000 ppm acetaldehyde for 90 weeks. H&E, $\times 16$.

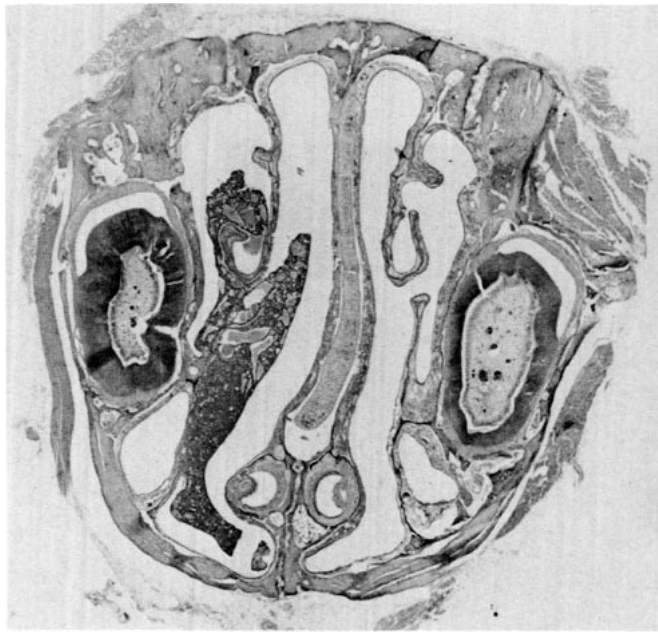


PLATE 5. Sessile polypoid adenoma originating from the maxilloturbinate and lateral wall; male rat exposed to 20 ppm formaldehyde for 4 weeks and killed after a recovery period of over 2 years. H&E, $\times 10$.

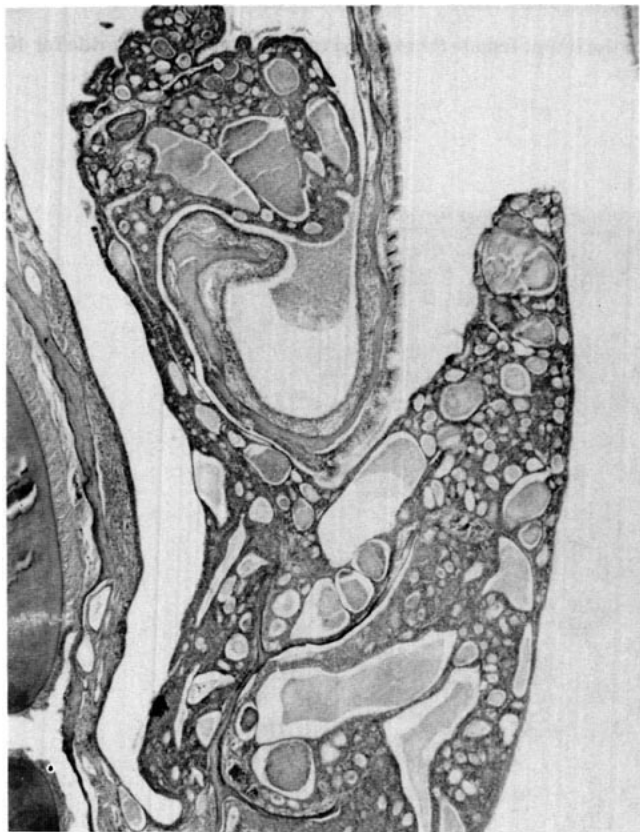


PLATE 6. Polypoid adenoma; higher magnification of the tumor depicted in Plate 5. H&E, $\times 40$.

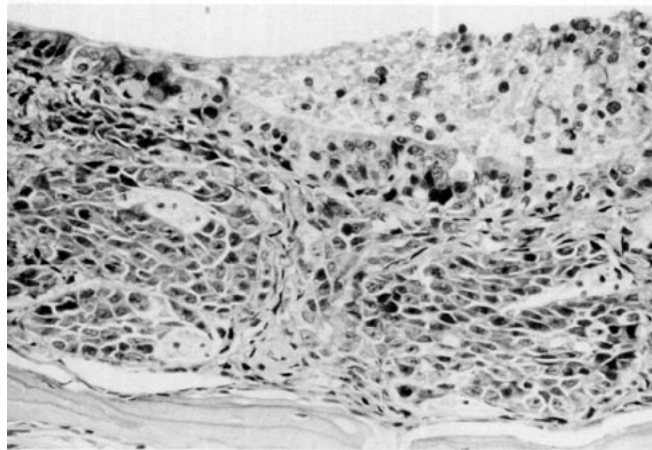


PLATE 7. Adenocarcinoma of the olfactory epithelium; male rat exposed to 5000 ppm vinyl chloride for 52 weeks. H&E, $\times 400$.



PLATE 8. Adenocarcinoma of the olfactory epithelium containing areas of dark and light cells; male rat exposed to 750 ppm acetaldehyde for 28 months. H&E, $\times 7$.

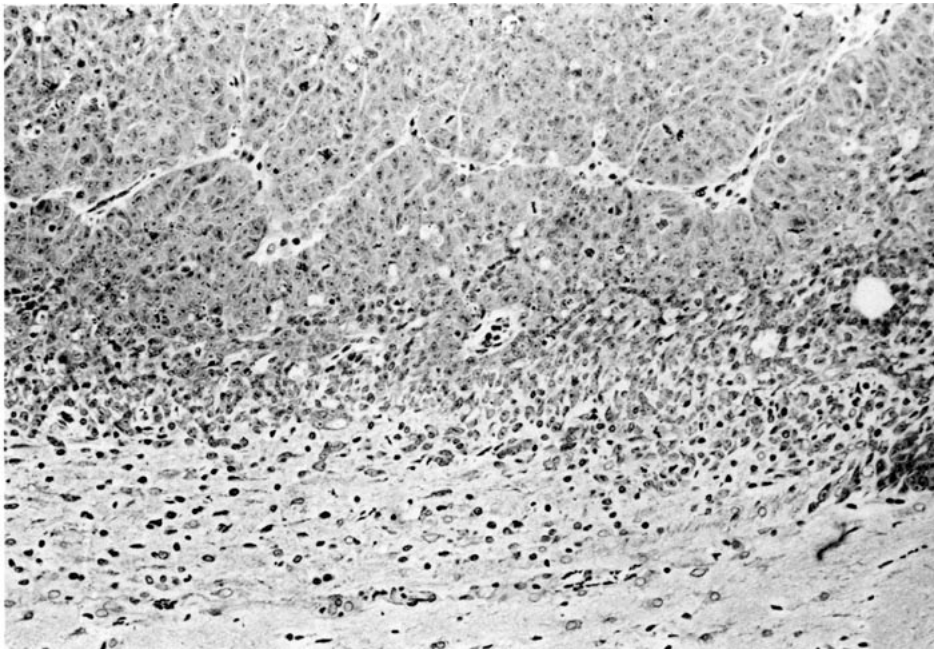


PLATE 9. Extension of an adenocarcinoma of the olfactory epithelium into the brain; female rat exposed to 5000 ppm vinyl chloride for 46 weeks. Reticulin stain, $\times 400$.

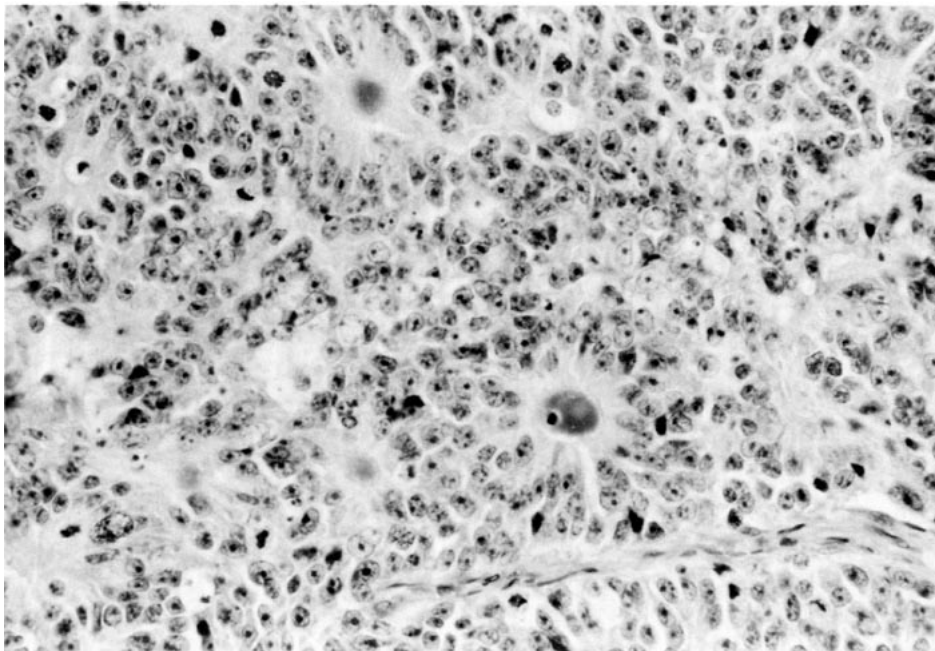


PLATE 10. Adenocarcinoma of the olfactory epithelium exhibiting rosettes and "owl eye" nuclei; female rat exposed to 1000/3000 ppm acetaldehyde for 88 weeks. H&E, $\times 400$.

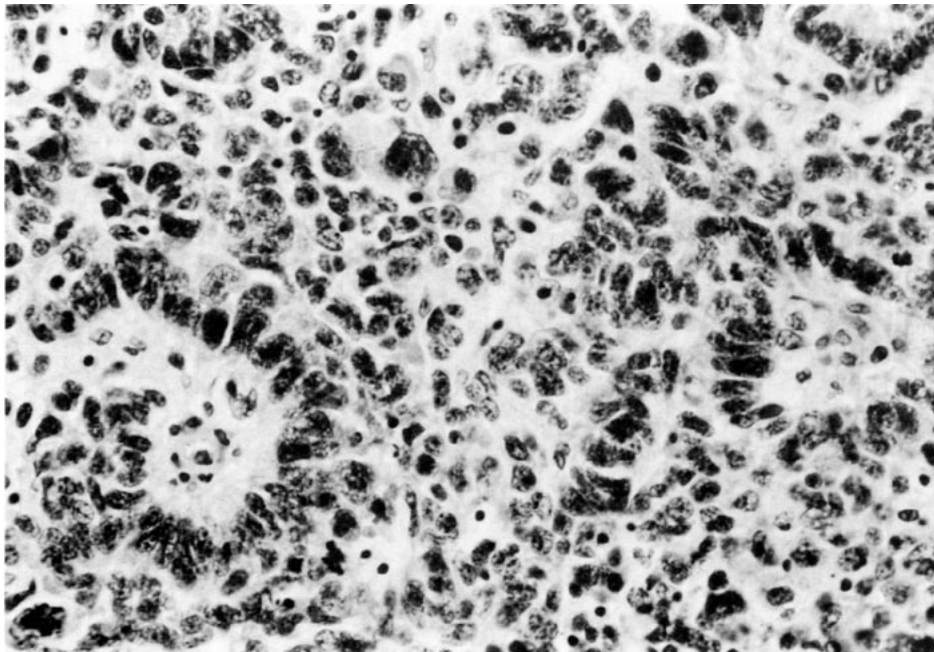


PLATE 11. Adenocarcinoma of the olfactory epithelium extending into the brain and exhibiting pseudorosettes and pleomorphic, hyperchromatic nuclei; female rat exposed to 1500 ppm acetaldehyde for 107 weeks. H&E, $\times 400$.

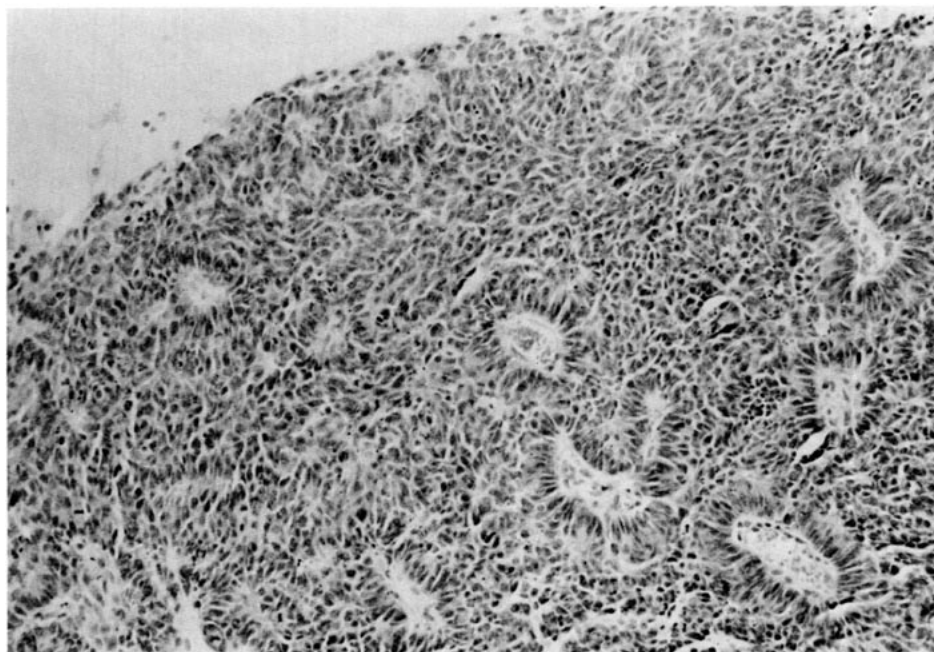


PLATE 12. Adenocarcinoma of the olfactory epithelium exhibiting pseudorosettes and elongated cells; male rat exposed to 1000/3000 ppm acetaldehyde for 96 weeks. H&E, $\times 160$.

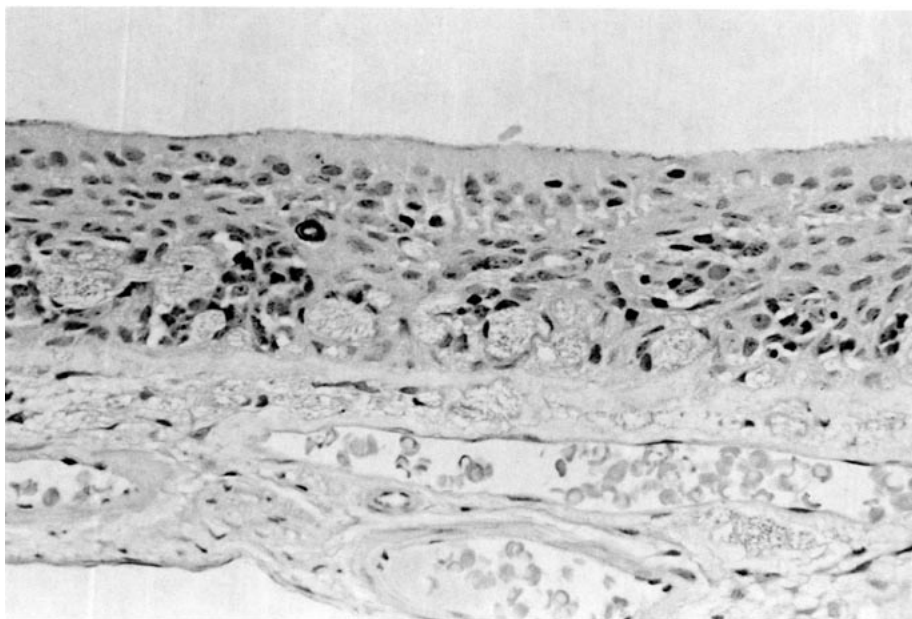


PLATE 13. Regeneration of olfactory epithelium seen as a thick layer of disarranged cells, most probably consisting of basal cells, sustentacular cells, sensory cells, and cells in various stages of differentiation. Foamy structures resembling early nerve bundles are visible above the markedly thickened basal lamina; male rat exposed to 1500 ppm acetaldehyde for 52 weeks and killed after a recovery period of 26 weeks. H&E, $\times 400$.

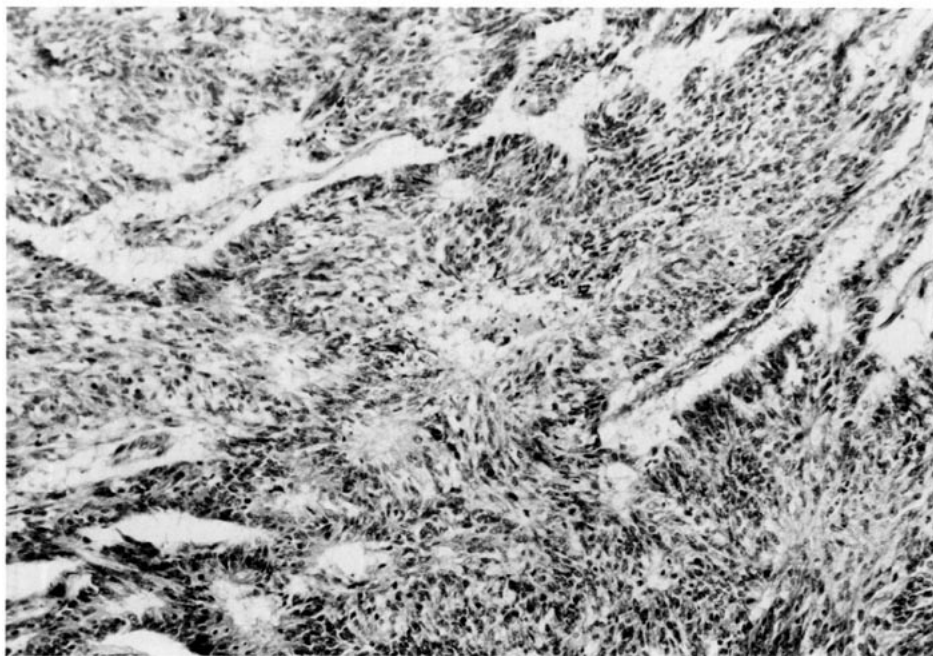


PLATE 14. Tumor of the olfactory epithelium classified as an esthesioneuroepithelioma. Note the abundance of columnar cells arranged in rosettes; male rat exposed to 5000 ppm vinyl chloride for 40 weeks. H&E, $\times 160$.

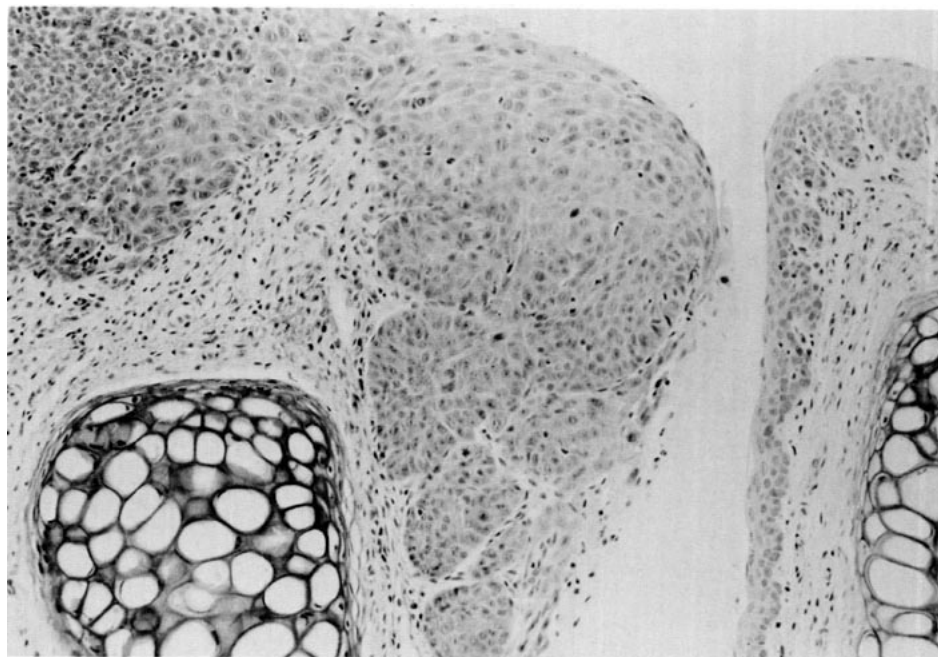


PLATE 15. Carcinoma *in situ* of the larynx; female rat exposed to 1500 ppm acetaldehyde for 122 weeks. H&E, $\times 160$.